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DARLENE A VANSTONE
IMMUNOLOGIC PHARMACEUTICAL CORPORATION
PATENT DEPARTMENT
610 LINCOLN STREET
WALTHAM MA 02154

EXAMINER	
CAPUTA, A	
ART UNIT	PAPER NUMBER
1806	

DATE MAILED: 09/23/96

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary	Application No. 08/226,248	Applicant(s) Griffith et al.
	Examiner Anthony C. Caputa	Group Art Unit 1806

☒ Responsive to communication(s) filed on *May 31, 1996*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-12, 40, 61, and 122-137* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *1-3, 6-12, 122, and 123* is/are allowed.

☒ Claim(s) *4, 5, 40, 61, and 124-137* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Part III DETAILED ACTION

Election/Restriction

1. Applicant's election of Group I, claims 1-12 and 61 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement (Paper No. 10), the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)). Upon further consideration by the Examiner the election of species is withdrawn.

2. Claims 13-39, 41-60, and 62-121 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention was made **without** traverse in Paper No. 10.

Claim Rejections - 35 USC § 112

3. The prior rejection of claims 1-12, 40, and 61 under 35 U.S.C. § 112, second paragraph, is withdrawn in view of applicants' amendment.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach one of ordinary skill in the art how to make and use the claimed invention, i.e. failing to provide an enabling disclosure.

a. The specification provides insufficient guidance to a nucleic acid coding for the Cry I j species as broadly claimed which encompass modifications (i.e. deletions, additions, functional equivalents, or fragments). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of deletions, additions, or modifications broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. The amino acid sequence of a protein determines its structural and functional properties, and the predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. While recombinant and mutagenesis techniques are known, it is **not** routine in the art to screen for positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure. One skilled in

the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple deletions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. Bowie et al. (Science 247:1306-1310) teach positions in the sequence that are critical to the protein's structure/function relationship, can tolerate only relatively conservative substitutions or no substitutions (see pages 1306-1310, especially p. 1306, column 2). Furthermore Kumar et al. (PNAS 87:1337-1341 1990) teach amino acid variations at a single residue of a peptide can affect T cell activation and other properties. The specification does not support the broad scope of the claims because the specification does **not** disclose the specific positions which can be predictably modified and which regions are critical.

Thus, applicants have **not** provided sufficient guidance to enable one skilled in the art to make and use the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of deletions of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the proteins structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200,

18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027, Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986), and Ex parte Anderson, 30 USPQ 2d 1866 (Bd. Pat. App. & Int. 1993).

Upon further consideration by the Examiner the enablement rejection is withdrawn for claims 1-3, 6-9. However for claims 4, 5, and newly added claims 126-137 the rejection is maintained.

Applicants assert the antigenic fragmetns can be determined by methods in the art and as taught in the spepcification. Stern and Berzofsky teach of the problems of predicting antigenic sites on proteins. Stern et al. teaches that problems of predicting antigenic sites are, whether all antigenic sites on the protein in question have been found (see page 166, Column 2 and 3). It would have been expected that the prior art would have only found a subset and not all immunogenic determinants (i.e. fragments that are non-contiguous and conformation dependent). Berzofsky et al. teaches that although intrinsic factors (i.e. hydrophilicity) may determine the repertoire of potential antigenic sites, only a subset will be immunogenic in a host because (see page 937 and 939) of such host factors as tolerance, immune response genes, clonal preemption, etc. Fox et al. teaches there methods for identifying antigenic determinants are unpredictable, because there is no reliable method which determines which linear segments are accessible to the host's immune system and linear peptides do not mimic the secondary and tertiary structures (see Columns 3, and 5-20). Because not all fragments that contain the immunogenic determinants can be predicted by the prior art and factors in the host influence

which determinants are immunogenic it would require undue experimentation to determine which fragments contain immunogenic determinants as claimed.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various positions or regions directly involved with binding. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., Science, Vol 247, pp 1306-1310, especially p. 1306, column 2, paragraph 2). Applicants have provided no guidance to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. amino acid substitutions), and the nature and extent changes that can be made in these positions. See Ex parte Forman, 230 USPQ 546 (Bd Pat. App. & Int. 1986).

Applicants state that they are enabled for functional equivalents in view the specifcation expalins and taches what are functional equivalents.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a

substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al.). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). These references demonstrate that a even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Applicants have provided no guidance to enable on of ordinary skill in the art to determine, without undue experimentation, the effects of different amino acid substitutions and the nature and extent of changes that can be made. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

b. The specification describes the nucleic acid sequence coding for *Cry j* I and the deduced amino acid sequence (page 7). The specification teaches the purification and cloning of Cry j I. The specification also discloses peptides of Cry j I that have T cell stimulating activity. The specification disclose binding assays of IgE to purified and recombinant Cry j I and histamine release analysis. The specification does not identify particular antigenic fragments that modify B cell responses. The specification does not identify particular antigenic fragments that bind IgE but do not result in mediator release. The specification also does not identify which modifications to *Cry j* I would result in the reduction of an allergic response following the administration of the modified *Cry j* I. The specification also does not identify fragments or proteins of the peptides having T cell epitopes of *Cry j* I or any of the other properties listed above. In the absence of evidence to the contrary, it would require undue experimentation to test the isolate the

nucleic acid encoding the *Cry j* I fragments, functional equivalents, or peptides for the properties listed above.

Applicants argue that this rejection should be withdrawn in view the limitation considered are withdrawn from consideration. Applicants argumetns are acknowledeged. However, it is the Examiner posiiton that since the claimed invneiton encompasss said limitations that to overcome the rejection applicant amend the claims that it does not read on the non-elelcted invention.

5. Claims 4, 5, 40, 61, and newly added claims 124-137 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

6. Claims 132 and 134 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 132 and 134 are vague and indefinte since it is not clear what constitues as "high homology".

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Anthony C. Caputa, whose telephone number is (703)-308-3995. The examiner can be reached on Monday-Thursday from 8:30 AM-6:00 PM.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703)-308-0196.

Papers related to this application may be submitted to Art Unit 1806 by facsimile transmission. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The Fax number is (703)-305-3014.

Anthony C. Caputa, Ph.D.

November 25, 1995

ACC

ANTHONY C. CAPUTA
PRIMARY EXAMINER
GROUP 1800